Controversies in the Management of Oropharynx Cancer

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Abstract
Squamous cell carcinomas of the oropharynx account for approximately 25% of all head and neck squamous cell malignancies. Most patients present with locally advanced tumors and require a multimodality approach to treatment, with input from qualified surgeons and radiation and medical oncologists. For organ preservation, concurrent chemoradiotherapy is usually preferred over surgery with adjuvant radiotherapy. Controversies regarding management of particular populations of locally advanced oropharyngeal tumors exist, including whether to include induction chemotherapy before chemoradiation, the use of biologic agents as radiation sensitizers, and how best to manage the neck after definitive treatment. Additionally, infection with human papilloma virus (HPV), particularly HPV-16, is now an established risk factor for head and neck cancer. Most cases involve the oropharynx, and prognosis seems to be much better than for patients with non–HPV- and tobacco-related tumors. Given the distinct differences between these HPV and non–HPV-related cancers, controversy also exists regarding the management of these patient populations, with the concern that HPV-related malignancies may be overtreated. Unfortunately, these and other questions concerning the management of locally advanced oropharyngeal cancers are outstanding. Hence, it is critical that eligible patients are screened for and encouraged to participate in clinical trials. (JNCCN 2008;6:707–714)

Head and neck squamous cell carcinoma (HNSCC) accounted for 34,360 newly diagnosed cancer cases in 2007, with 7550 attributable deaths in the United States alone.1 Worldwide, approximately 123,000 cases of oropharyngeal and hypopharyngeal cancer are diagnosed each year, resulting in approximately 79,000 deaths.2 Oropharyngeal squamous cell carcinomas (OSCCs) generally refer to tumors involving the soft palate, tonsils, base of tongue, and vallecula.3 OSCC is 3 times more common in men than women, with most cases occurring in the fifth to seventh decades of life,4 although the average age at diagnosis is trending downward.5

Tobacco and alcohol are the principal risk factors for OSCC. Compared with the general population, smoking increases the risk for HNSCC by approximately 5 times in men and 12 times in women;6 heavy alcohol consumption (>3 drinks daily) doubles the risk.7 Infection with human papilloma virus (HPV), especially HPV-16, is contributing to the marked increase in the number of OSCC cases. Since the early 1970s, the incidence of tonsillar and base-of-tongue cancers has continued to rise steadily by approximately 4% and 2% per year, respectively.8 The prevalence of HPV-positive OSCC steadily increased from 20% in the 1970s to more than 60% in the 2000s.9 Oral HPV-16 infection is positively associated with OSCC, and viral exposure correlates with increasing numbers of oral sexual partners.10 Finally, a diet poor in fruits and vegetables elevates risk.10

Early-stage OSCCs are treated primarily with surgery or radiation therapy with similar rates of disease control and survival.11 However, some patients with stage II disease may require more attention to their necks because of concern for nodal micrometastasis. More sensitive immunohistochemical methods of nodal examination have reclassified negative neck nodes as positive in approximately 20% of cases.12 Treatment of locally advanced OSCC (stages III and IVA/B) is more complicated and...
requires a multidisciplinary team approach to provide optimal therapy. In general, combined surgery and adjuvant radiation therapy\textsuperscript{13} or concurrent chemoradiation\textsuperscript{14,15} are accepted standard therapies for patients with locally advanced tumors. Nonetheless, controversies exist regarding the management of particular populations of locally advanced oropharyngeal tumors. This article focuses on various controversial areas of medical and surgical management in patients with OSCC.

**Management of Locally Advanced OSCC**

Patients with locally advanced tumors have T3 to T4 disease or nodal involvement without distant metastases, including smaller primaries with N1 disease (i.e., T2, N1 tumors). T4 tumors invade neighboring structures such as the larynx, palate, mandible, pterygoid muscle and plates, and lateral nasopharynx or encase the carotid artery. Treatment for these tumors is generally based on whether they are amenable to surgery. Unresectable disease (i.e., tumors invading the skull base or encasing the carotid arteries) is usually treated with combined chemoradiotherapy. However, surgically resectable disease, in which the surgeon expects to achieve gross removal of the entire tumor with acceptable functional and cosmetic preservation, may be treated with organ sparing methods or with bimodality surgical and radiation approaches.

**Surgical Versus Nonsurgical Approaches in Resectable Disease**

The selection of patients for definitive chemoradiotherapy versus primary surgery for locally advanced OSCC is complex and requires a multidisciplinary team. As stated in the NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancers (in this issue; to view the most recent version, visit the NCCN Web site at www.nccn.org),\textsuperscript{14} the preferred (category 1) treatment for patients with T3–4a, N0/N+ or any T, N2–3 OSCC is concurrent chemoradiotherapy (see pages 655 and 656). Other options include surgery followed by radiation (or chemoradiotherapy for patients with adverse features), induction chemotherapy followed by chemoradiotherapy (category 3), or treatment in a multimodality clinical trial. Currently, no prospective randomized trials compare combined chemoradiotherapy with primary surgery and radiation, although long-term quality of life seems to be similar with either modality.\textsuperscript{17} Therefore, the decision to treat patients with a particular modality depends on input from the patient, surgeon, and medical and radiation oncologists.

In patients selected for treatment with chemoradiation, a platinum-based regimen remains the standard of care\textsuperscript{18,19} with different treatment schedules ranging from daily cisplatin\textsuperscript{20} to high-bolus doses of cisplatin every 3 weeks.\textsuperscript{21,22} However, the optimal platinum dosing schedule is difficult to determine. Carboplatin is also efficacious as a radiation sensitizer and has been used with and without 5-fluorouracil (FU) in concurrent chemoradiotherapy regimens to treat patients with OSCC.\textsuperscript{23–25}

**Biologic Agents as Radiation Sensitizers**

Epidermal growth factor receptor (EGFR) is highly overexpressed in HNSCC and associated with a worse prognosis.\textsuperscript{26,27} Its activation promotes metastasis by increasing motility and adhesion of tumor cells, promoting angiogenesis and proliferation.\textsuperscript{28} Cetuximab is a recombinant monoclonal antibody that competitively inhibits natural ligands of EGF through binding to the receptor itself, thus preventing phosphorylation and activation of downstream kinases.\textsuperscript{29}

Bonner et al.\textsuperscript{30} randomized patients with advanced HNSCC to radiotherapy with or without cetuximab, an anti-EGFR monoclonal antibody; more than 50% of patients in each treatment arm had OSCC. The treatment arms showed similar toxicities, except for the incidence of rash, which was greater in the cetuximab arm (17% vs. 1%). Compared with radiotherapy alone, the addition of cetuximab increased the duration of locoregional control and rates of overall and progression-free survival.

Although the combination of cetuximab and radiation seems to be an effective definitive treatment approach, especially for patients with OSCC, who constituted most of the study population, the comparison arm (radiation alone) is not the accepted standard for patients with locally advanced OSCC. Additionally, the authors used the Kaplan-Meier method to estimate locoregional control, whereby the duration was defined as “the time from randomization until the first documented progression or recurrence of locoregional disease, or until death from any cause.”\textsuperscript{30}

In doing so, they failed to report the cumulative incidence of locoregional failure, which raises the question...
as to whether local disease control was actually improved in the cetuximab arm. Finally, the authors reported similar distant metastatic rates at 1 or 2 years in both treatment arms, suggesting that cetuximab alone may not be enough to control tumor spread. This finding is especially important because distant failure rates are now increasing with combined chemoradiotherapy regimens despite excellent improvements in local control.

Because the toxicity profile of cetuximab and radiation is viewed as more tolerable than combined chemoradiation, some may consider it a substitute for chemoradiotherapy in elderly patients or those who are frail. However, others believe that the severity of radiation dermatitis and the risk for hypersensitivity reactions may be underreported in the Bonner et al. study, suggesting that cetuximab and radiation may not be such a “benign” regimen. A study from Vanderbilt University concluded that the rate of IgE-mediated hypersensitivity reactions to cetuximab infusions is much higher than previously reported in some areas of the United States. This difference seems to be related to serum IgE antibodies against cetuximab that were present before therapy.

Additionally, the meta-analyses by Bourhis et al. reported no benefit from combined chemoradiotherapy (compared with radiation) in patients older than 70 years. Hence, treatment with cetuximab and radiation may be viewed as an improvement over radiotherapy alone in these patients. The Bonner et al. study, however, did not specifically evaluate older patients or those with poor performance status; the median age was 56 years. Therefore, it cannot be assumed that elderly patients or those with comorbid conditions will gain any additional benefits from the addition of cetuximab to radiotherapy.

**Induction Chemotherapy Followed by Chemoradiation for Locally Advanced OSCC**

The use of induction chemotherapy (IC) outside the scope of a clinical trial remains highly debated among the NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancers Panel. To prove that IC should be incorporated into the management of locally advanced OSCC, proponents capitalize on improvements in locoregional and distant control of disease. IC may eradicate early micrometastatic disease and provide early symptomatic control.

Two trials reported in the 1990s and early 2000s showed an overall survival benefit with IC and data from the Meta-Analysis of Chemotherapy on Head and Neck Cancer showed a marginal improvement in survival ($P = .05$) with IC regimens containing cisplatin and 5-FU. These findings prompted some experts to review the use of IC with radiation and chemoradiotherapy.

Several practices in treating locally advanced HNSCC have led to improved locoregional control. Compared with conventional, once-daily fraction radiotherapy, hyperfractionated radiotherapy provides a 10% to 20% improvement in local control rates. Hyperfractionated radiotherapy, however, is not considered standard care for patients with OSCC and is associated with significant toxicity. Secondly, locoregional control is improved with the addition of chemotherapy to radiation. IC may augment this benefit through reducing the size of the primary tumor, thereby improving the efficacy of concurrent chemoradiotherapy. In addition, radiotherapy disrupts blood supply to the tumor bed, resulting in decreased chemoperfusion. IC may bypass this issue, allowing for greater tissue penetration before definitive chemoradiotherapy.

Despite improvements in locoregional disease control, the development of distant metastases remains an issue. To reduce distant failures, more-effective IC regimens have evolved, incorporating the use of taxanes. The EORTC compared cisplatin/5-FU with cisplatin/5-FU/docetaxel as induction regimens given before definitive radiotherapy. The triplet induction arm showed significant improvements in progression-free and overall survival. These results then set the stage for a randomized phase II study comparing IC with paclitaxel/5-fluorouracil/cisplatin versus cisplatin/5-FU followed by cisplatin-based chemoradiotherapy. The triplet combination showed better response rates and median time to treatment failure.

Similarly, Posner et al. compared docetaxel/5-FU/cisplatin with cisplatin/5-FU as induction regimens before treatment with concomitant carboplatin and radiotherapy. Response rates were higher in the triplet arm, and the 3-year survival rates were markedly better with the 3-drug regimen (62% vs. 48%).

The question remains whether IC followed by chemoradiotherapy improves survival over chemoradiotherapy alone. Early data presented at the American
Society of Clinical Oncology 2006 annual meeting suggest that IC may play a favorable role. In a randomized phase II study by Paccagnella et al., complete response (CR) rates after combined IC with chemoradiotherapy were 47%, compared with 20% in those undergoing immediate chemoradiotherapy alone.

In a second phase II/III study by Hitt et al., patients were randomized to 3 different arms: chemoradiotherapy alone, cisplatin/5-FU followed by chemoradiotherapy, and docetaxel/cisplatin/5-FU followed by chemoradiotherapy. CR rates were higher in the groups undergoing IC compared with chemoradiotherapy alone. These results are compelling and suggest that effective IC regimens may impact overall outcomes.

However, these preliminary data should be interpreted cautiously because they do not provide information on differences in survival. To definitively determine the benefit of IC, 2 large phase III trials from the Dana-Farber Cancer Institute and the University of Chicago are currently enrolling patients. Until definitive results from these trials are available, IC followed by chemoradiotherapy is not considered standard care for treating locally advanced HNSCC, and participation in clinical trials is crucial.

Additional concerns about the use of IC focus on the possible risk for increased toxicities with IC and the potential for overtreatment in HPV-related OSCC. Ioannidis and Lau showed that clinical trials often fail to document toxicity sufficiently. Other investigators have questioned the lack of systematic guidelines in reporting and analyzing adverse events, raising concern about the common practice of only reporting high-grade (III and IV) toxicities and minimizing low-grade (I and II) toxicities, which are often substantial.

The authors of the study also questioned whether clinicians are minimizing late toxicities, such as swallowing dysfunction and aspiration, in trials evaluating IC. With the addition of IC before concurrent chemoradiotherapy, increased toxicity is a concern, as reported by the increased rates of neutropenia in the triplet IC arms of randomized trials. In elderly patients and those with marginal performance statuses, excessive toxic effects may ultimately delay definitive therapy or hinder the ability to deliver adequate chemoradiotherapy.

Approximately 25% of OSCCs are HPV-related and occur in younger patients without extensive histories of alcohol or tobacco consumption. Molecular and epidemiologic data show a strong association between HPV-16 and cancers of the lingual and palatine tonsils, and studies have shown improved survival in patients with these HPV-related tumors. Based on these findings, it is prudent to consider whether all patients with locally advanced OSCC who are candidates for combined modality chemoradiation should be treated with the same intensity. Moreover, some believe that these tumors may not require IC to obtain locoregional control or improve survival. Therefore, further clinical investigations are warranted.

Management of the Neck After Definitive Local Therapy

The NCCN guidelines for OSCC recommend observation for patients with N1 disease who attain a complete clinical response in the neck, and neck dissection for those with clinically residual nodal disease. In patients with N2–3 disease, management of the neck after complete clinical response with chemoradiotherapy is controversial (category 3). The guidelines suggest either observation or neck dissection. Furthermore, major disagreement exists as to the type of dissection (i.e., category 3 for selective vs. comprehensive) if surgery is considered the primary treatment modality for OSCC.

Proponents of neck dissection after concurrent chemoradiotherapy argue that clinical parameters do not predict residual neck disease or risk for regional failures. McHam et al. attempted to correlate clinical characteristics of N2–3 neck after definitive chemoradiotherapy with pathologic complete response (pCR). They found no correlation between clinical complete response (cCR) and pCR, suggesting that all patients with N2–3 disease should undergo neck dissection. Additionally, others suggest that residual micrometastatic disease may not be detectable in patients with cCR and those with radiographic complete response (rCR), and also recommend planned neck dissections for all patients with N2–3 disease to avoid excessive morbidity associated with recurrence.

Those arguing against neck dissection for patients with cCR after chemoradiotherapy are concerned about surgical complications and quality of life issues. In one retrospective review, investigators noted wound complications in 22% of patients who underwent neck dissection. Complication rates, including greater skin flap necrosis, were even higher in those who received more than 70 Gy of preoperative radiation. Other quality
of life concerns include disfigurement and shoulder dysfunction associated with neck dissections.\(^6\)\(^6\)\(^7\)\(^1\)

Given the potential for longstanding surgical complications and that recurrence rates in the neck can be as low as 5% after chemoradiotherapy,\(^6\)\(^6\)\(^9\) many believe that patients with excellent radiographic responses should forgo neck dissection. For example, Liauw et al.\(^7\)\(^0\) found that rCR had a higher sensitivity and positive predictive value than cCR when attempting to identify residual nodal disease. In addition, these investigators found no differences in rates of locoregional control, disease-specific survival, or overall survival among patients who experienced rCR (and did not undergo neck dissection) compared with those who experienced pCR after neck dissection. Other published studies also show no differences in overall and progression-free survival in patients with N2–3 disease who had experienced cCR and underwent neck dissection and those who underwent observation only.\(^6\)\(^2\)\(^7\)

Fluorodeoxyglucose (FDG)-PET has been investigated in lymphoma and solid malignancies to test disease response.\(^7\)\(^2\)\(^3\) Retrospective and prospective studies in HNSCC have reported that FDG-PET has rather low sensitivity for predicting residual nodal disease.\(^7\)\(^4\)\(^7\)\(^9\) Investigators of these studies have recommended against using FDG-PET to select patients for neck dissection.

On the contrary, a recent study from the University of Pittsburgh noted a greater than 90% accuracy with FDG-PET, suggesting that negative PET-CT scans are highly reliable for the absence of residual cervical nodal disease.\(^8\)\(^0\) Nayak et al.\(^8\)\(^1\) performed needle biopsies of the neck after positive FDG-PET scans to confirm residual disease before neck dissection, showing a positive predictive value of 70% and negative predictive value of 97%.

No current definitive guidelines support or refute the use of FDG-PET in selecting patients with OSCC for neck dissection after experiencing cCR at the primary disease site and in the neck after chemoradiotherapy. Because of a lack of definitive evidence from prospective, randomized clinical trials, management of the neck with observation (CT-PET) versus planned neck dissection remains a category 3 recommendation per the NCCN guidelines.

When surgery is considered the primary treatment option for patients with OSCC and N2–3 disease, whether a modified radical neck dissection (MRND) or a selective neck dissection (SND) should be performed remains controversial. Ambrosch et al.\(^8\)\(^2\) published a large retrospective review of patients with HNSCC and N0–2 disease. They suggested that 3-year rates of neck recurrence for pN1 and pN2 after SND were similar to historical controls who underwent MRND. Others suggest that SND is adequate in patients with pathologic node-positive neck disease only if postoperative radiation therapy is administered.\(^8\)\(^3\) Leemans and Snow,\(^8\)\(^4\) however, combined several large studies of elective SND and MRND and found a statistically significant lower recurrence rate with pathologically positive neck nodes in patients treated with MRND versus SND.

Although no randomized, prospective trials have compared SND with MRND, most experts would agree that nodal fixation, disease larger than 3 cm, and presence of extracapsular extension require treatment with an MRND. Given the lack of prospective data supporting SND in patients with N2–3 disease, its use in clinical practice requires excellent judgment and technical skill on behalf of the treating surgeon.

Conclusions

Treatment of locally advanced OSCC is complex and requires input from a multidisciplinary head and neck oncology team. Currently, the preferred treatment for T3–4a, N0/N+ or any T, N2–3 OSCC is combined chemoradiotherapy using a platinum-based chemotherapy regimen. Other options include bimodality surgery and radiotherapy, the addition of IC to chemoradiotherapy, or enrollment in a multimodality clinical trial. However, the NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancers Panel members have conflicting medical and surgical opinions regarding these treatment options. Controversial areas focus on a lack of definitive data comparing treatment paradigms. Additionally, HPV-related OSCC is a growing epidemic for which an ideal treatment has not been determined. With this changing population of patients and the many outstanding questions, most experts agree that enrollment of patients in clinical trials is preferred.

References


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